

US-PAT-NO: 6248516

DOCUMENT-IDENTIFIER: US 6248516 B1

TITLE: Single domain ligands, receptors comprising said ligands methods for their production, and use of said ligands and receptors

DATE-ISSUED: June 19, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE
COUNTRY			
Winter; Gregory Paul	Cambridge	N/A	N/A
GBX			
Ward; Elizabeth Sally	Cambridge	N/A	N/A
GBX			
Gussow; Detlef	Abington	N/A	N/A
GBX			

US-CL-CURRENT: 435/6,435/252.33 , 435/441 , 435/446 , 435/69.6

CLAIMS:

What is claimed is:

1. A library for expression of immunoglobulin heavy chain variable domains (VH domains), said library comprising a repertoire of nucleic acid sequences encoding a third CDR of an immunoglobulin heavy chain variable domain, each member of said repertoire being flanked by VH sequences so as to provide nucleic acid encoding a repertoire of immunoglobulin heavy chain variable domains which are identical except for said third CDR.
2. A library according to claim 1 wherein said third CDRs are derived from preexisting repertoires of CDRs.
3. A library according to claim 1 wherein said third CDRs comprise random sequences.
4. A library according to claim 1 wherein said nucleic acid encoding a repertoire of immunoglobulin heavy chain variable domains further comprises a sequence encoding one or more constant domains for expression of Ig-type chains.
5. A method for generating an antibody variable domain expression library having a diversity of CDR3 sequences, said method comprising: providing expression vectors, said vectors comprising a variable domain encoding sequence of an antibody; introducing by mutagenesis a diversity of CDR3 sequences into

said variable domain
encoding sequence; and
recovering an expression library having a diversity of binding
activities.

6. The method of claim 5 wherein said antibody variable domain
is a VH domain.

7. The method of claim 5 wherein said expression vector encodes
an Fab antibody
fragment.

8. The method of claim 5 wherein said expression vector encodes
a scFv fragment.

9. An expression library which expresses antibody variable
domains, said library
comprising a universal set of framework regions carrying a
diversity of CDR3
sequences, said library having a diversity of binding activities.

10. The expression library of claim 9 wherein said antibody
variable domains are VH
domains.

11. The expression library of claim 9 wherein said antibody
variable domains are VL
domains.

12. The expression library of claim 9 wherein said variable
domains are expressed
in the form of Fab antibody fragments.

13. An expression library which expresses antibody variable
domains having CDR
diversity in only the CDR3 sequences, said library having a
diversity of binding
activities.

14. The expression library of claim 13 wherein said antibody
variable domains are
VH domains.

15. The expression library of claim 13 wherein said antibody
variable domains are
VL domains.

16. The expression library of claim 13 wherein said variable
domains are expressed
in the form of Fab antibody fragments.

17. The expression library of claim 13 wherein said variable
domains are expressed
in the form of scFv antibody fragments.

18. An expression library produced by the method of claim 5.

19. An expression library produced by the method of claim 6.

20. An expression library produced by the method of claim 7.

21. An expression library produced by the method of claim 8.

US-PAT-NO: 6225447

DOCUMENT-IDENTIFIER: US 6225447 B1

TITLE: Methods for producing members of specific binding pairs

DATE-ISSUED: May 1, 2001

INVENTOR-INFORMATION:

NAME COUNTRY	CITY	STATE	ZIP CODE
Winter; Gregory Paul GBX	Cambridge	N/A	N/A
Johnson; Kevin Stuart GBX	Cambridge	N/A	N/A
Griffiths; Andrew David GBX	Cambridge	N/A	N/A
Smith; Andrew John GBX	Cambridge	N/A	N/A

Hammond

US-CL-CURRENT: 530/387.3

CLAIMS:

What is claimed is:

1. A specific binding pair member which is a single chain specific binding pair member comprising a first polypeptide chain component and a second polypeptide chain component and specific for a complementary specific binding pair member of interest, produced by a method which comprises:
 - (I) introducing into host cells;
 - (i) first vectors comprising nucleic acid encoding a genetically diverse population of a first polypeptide chain component fused to a component of a secreted replicable genetic display package for display of said polypeptide chain component at the surface of replicable genetic display packages; and
 - (ii) second vectors comprising nucleic acid encoding a genetically diverse population of said second polypeptide chain component; said first vectors being packaged in infectious replicable genetic display packages and their introduction into host cells being by infection into host cells harboring said second vectors; or
 - said second vectors being packaged in infectious replicable genetic display packages and their introducing into host cells being by infection into host cells harboring said first vectors;

(II) causing or allowing recombination between said first and second vectors within said host cells, the recombination being promoted by inclusion in said first and second vectors of sequences at which site-specific recombination occurs resulting in recombinant vectors each of which comprises nucleic acid encoding a said single chain specific binding pair member comprising a said first polypeptide chain component and a said second polypeptide chain component and an amino acid sequence encoded by a sequence provided by recombination between said sequences at which site-specific recombination occurs, and capable of being packaged into a replicable genetic display packages using said replicable genetic display package component;

(III) expressing said single chain specific binding pair members within the host cells to form a library of said single chain specific binding pair members displayed by replicable genetic display packages, whereby the genetic materials of each said replicable genetic display package encodes a single chain specific binding pair member displayed at its surface,

(IV) selecting by binding with said complementary specific binding pair member of interest one or more single chain specific binding pair members specific for said complementary specific binding pair member of interest, each single chain specific binding pair member thus selected being associated in its respective replicable genetic display package with nucleic acid encoding that single chain specific binding pair member,

(V) obtaining nucleic acid encoding a said single chain specific binding pair member from its replicable genetic display package displaying a single chain specific binding pair member selected in step (IV);

(V) producing, by expression of encoding nucleic acid in a recombinant host organism, a single chain specific binding pair member comprising a first polypeptide chain component and a second polypeptide chain component and an amino acid sequence encoded by a sequence provided by recombination between said sequences at which

site-specific recombination occurs and specific for said complementary specific binding pair member of interest, which single chain specific binding pair comprises a polypeptide chain component which is as encoded by nucleic acid encoding a said polypeptide chain component of a specific binding pair member selected in step (IV) or is a derivative thereof by way of addition, deletion, substitution or insertion of one or more amino acids or by linkage of another molecule.

2. A specific binding pair member according to claim 1 wherein at least one of said first and second vectors is a phage vector.

3. A specific binding pair member according to claim 1 wherein expression in said step (III) is from a phagemid vector, the method including using a helper phage or a plasmid expressing complementing phage genes, to help package said phagemid genome, and said component of the replicable genetic display package is a capsid protein therefor.

4. A specific binding pair member according to claim 1 wherein either or both of the populations of said first and second polypeptide chain components is derived from a repertoire selected from the group consisting of:

- (i) the repertoire of rearranged immunoglobulin genes of an animal immunized with a complementary sbp member;
- (ii) the repertoire of rearranged immunoglobulin genes of an animal not immunized with a complementary sbp member;
- (iii) a repertoire of an artificially rearranged immunoglobulin gene or genes;
- (iv) a repertoire of an immunoglobulin homolog gene or genes;
- (v) a repertoire of sequences derived from a germ-line immunoglobulin gene or genes;
- (vi) a repertoire of an immunoglobulin gene or genes artificially mutated by the introduction of one or more point mutations; and
- (vii) a mixture of any of (i), (ii), (iii), (iv), (v) and (vi).

5. A specific binding pair member according to claim 1 wherein the replicable genetic display package is a bacteriophage, the host is a bacterium, and said component of the replicable genetic display package is a capsid protein for the bacteriophage.

6. A specific binding pair member according to claim 5 wherein

the phage is a
filamentous phage.

7. A specific binding pair member according to claim 6 wherein
the phage is
selected from the class I phages fd, M13, Ifl, Ike, ZJ/Z, Ff and
the class II phages
Xf, Pf1 and Pf3.

8. A specific binding pair member according to claim 6 wherein
the first
polypeptide chain components are expressed as fusions with the
gene III capsid
protein of phage fd or its counterpart in another filamentous
phage.

9. A specific binding pair member according to claim 8 wherein
the first
polypeptide chain components are each inserted in the N-terminal
region of the
mature capsid protein downstream of a secretory leader peptide.

10. A specific binding pair member according to claim 5 wherein
the first
polypeptide chain components are expressed as fusions with the
gene III capsid
protein of phage fd or its counterpart in another filamentous
phage.

11. A specific binding pair member according to claim 10 wherein
the first
polypeptide chain components are each inserted in the N-terminal
region of the
mature capsid protein downstream of a secretory leader peptide.

12. A specific binding pair member according to claim 5 wherein
the host is E.

coli.

13. A specific binding pair member according to claim 1, wherein
said sequences at
which site-specific recombination occurs are loxP sequences.

14. A specific binding pair (sbp) member which is a single chain
specific binding

pair member specific for a counterpart specific binding pair
member of interest,

produced by a method which comprises:

(i) causing or allowing intracellular recombination between (a)
first vectors

comprising nucleic acid encoding a population of a fusion of a
first polypeptide

chain component of a specific binding pair member and a component
of a secreted

replicable genetic display package and (b) second vectors
comprising nucleic acid

encoding a population of a second polypeptide chain component of
a specific binding

pair member, at least one of said populations being genetically

diverse, the recombination between the vectors being at sequences at which site-specific recombination occurs and resulting in recombinant vectors each of which comprises nucleic acid encoding a single chain specific binding pair member comprising a said first polypeptide chain component, a said second polypeptide chain component, and an amino acid sequence encoded by a sequence provided by recombination between said sequences at which site-specific recombination occurs, which nucleic acid is capable of being packaged using said replicable genetic display package component; and

(ii) expressing said single chain specific binding pair members producing replicable genetic display packages which display at their surface said single chain specific binding pair members and which each comprise nucleic acid encoding a said single chain specific binding pair member

(iii) selecting by binding with said counterpart specific binding pair member of interest one or more single chain specific binding pair members specific for said counterpart specific binding pair member of interest, each single chain specific binding pair member thus selected being associated in its respective replicable genetic display package with nucleic acid encoding that single chain specific binding pair member;

(iv) obtaining nucleic acid encoding a said single chain specific binding pair member from its replicable genetic display package displaying a specific binding pair member selected in step (v);

(v) producing, by expression of encoding nucleic acid in a recombinant host organism, a said single chain specific binding pair member comprising a first polypeptide chain component and a second polypeptide chain component and an amino acid sequence encoded by a sequence provided by recombination between said sequences at which site specific recombination occurs and specific for said complementary specific binding pair member of interest, which single chain specific binding pair comprises a polypeptide chain component which is as encoded by

nucleic acid encoding
a said polypeptide chain component of a specific binding pair
member selected in
step (v) or is a derivative thereof by way of addition, deletion,
substitution or
insertion of one or more amino acids or by linkage of another
molecule.

15. A specific binding pair member according to claim 14 wherein
the sequences at
which site-specific recombination occurs are loxP sequences and
site-specific
recombination is catalysed by Cre-recombinase.

16. A specific binding pair member according to claim 14 wherein
the first vectors
are phages or phagemids and the second vectors are plasmids, or
the first vectors
are plasmids and the second vectors are phages or phagemids, and
the intracellular
recombination takes place in a bacterial host which replicates
plasmids
preferentially over phages or phagemids, or which replicates
phages or phagemids
preferentially over plasmids.

17. A specific binding pair member according to claim 16 wherein
said bacterial
host is a PolA strain of *E. coli* or of another gram-negative
bacterium.

18. A specific binding pair member according to claim 17 which
comprises an
antibody antigen-binding domain.

19. A specific binding pair member according to claim 14 which
comprises a single
chain Fv immunoglobulin molecule.

US-PAT-NO: 6172197

DOCUMENT-IDENTIFIER: US 6172197 B1

TITLE: Methods for producing members of specific binding pairs
DATE-ISSUED: January 9, 2001

INVENTOR-INFORMATION:

NAME COUNTRY	CITY	STATE	ZIP CODE
McCafferty; John GBX	Sawston	N/A	N/A
Pope; Anthony Richard GBX	Cambridge	N/A	N/A
Johnson; Kevin Stuart GBX	Cambridge	N/A	N/A
Hoogenboom; Henricus GBX	Cambridge	N/A	N/A
Renerus Jacobus GBX	Cambridge	N/A	N/A
Mattheus GBX	Cambridge	N/A	N/A
Griffiths; Andrew David GBX	Cambridge	N/A	N/A
Jackson; Ronald Henry GBX	Cambridge	N/A	N/A
Holliger; Kaspar GBX	Cambridge	N/A	N/A
Philipp GBX	Buckingham	N/A	N/A
Marks; James David GBX	Cambridge	N/A	N/A
Clackson; Timothy Piers GBX	Cambridge	N/A	N/A
Chiswell; David John Winter; Gregory Paul Bonnert; Timothy Peter			
US-CL-CURRENT: 530/387.3, 435/235.1, 435/320.1, 435/6, 435/69.1 , 435/7.1, 530/387.1 , 530/412, 530/867, 536/23.1, 536/23.4, 536/23.53			

CLAIMS:

What is claimed is:

1. A library of filamentous bacteriophage particles displaying on their surface as a fusion with a gene III coat protein surface component a genetically diverse population of specific binding pair members in functional form comprising a binding domain for complementary binding specific binding pair members, said specific

binding pair members encoded by nucleic acid derived from a natural repertoire of nucleic acids encoding said genetically diverse population of specific binding pair members, the particles each containing a phagemid genome which is plasmid nucleic acid containing a single stranded phage replication origin and a nucleotide sequence encoding said fusion, and the particle having a coat partially derived from a helper phage and partly from said fusion.

2. A library according to claim 1 wherein the specific binding pair members comprise a binding domain of an immunoglobulin.

3. A library according to claim 2 wherein the specific binding pair members are scFv molecules.

4. A library according to claim 2 wherein the specific binding pair members comprise Fab molecules.

5. The library of claims 2, 3, or 4 wherein the natural repertoire of specific binding pair members is encoded by nucleic acid derived from an animal unimmunized against the complementary specific binding pair member.

6. The library of claims 2, 3, or 4 wherein the natural repertoire of specific binding pair members is encoded by nucleic acid derived from an animal immunized against the complementary specific binding pair member.

US-PAT-NO: 6140471

DOCUMENT-IDENTIFIER: US 6140471 A

TITLE: Methods for producing members of specific binding pairs

DATE-ISSUED: October 31, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE
COUNTRY			
Johnson; Kevin Stuart	Cambridge	N/A	N/A
GBX			
Winter; Gregory Paul	Cambridge	N/A	N/A
GBX			
Griffiths; Andrew David	Cambridge	N/A	N/A
GBX			
Smith; Andrew John	Cambridge	N/A	N/A
GBX			
Hammond	Canberra	N/A	N/A
AUX			
Waterhouse; Peter			
Michael			

US-CL-CURRENT: 530/387.3

CLAIMS:

What is claimed is:

1. A specific binding pair member which is a single chain specific binding pair member comprising a first polypeptide chain component and a second polypeptide chain component and which is specific for a complementary specific binding pair member of interest, produced by a method having the following steps:
(a) introducing into prokaryotic host cells
(i) first vectors comprising nucleic acid encoding a genetically diverse population of said first polypeptide chain component fused to a component of a secreted replicable genetic display package for display of said polypeptide chain components at the surface of replicable genetic display packages; and
(ii) second vectors comprising nucleic acid encoding a genetically diverse population of said second polypeptide chain components; said first vectors being packaged in infectious replicable genetic display packages and their introduction into prokaryotic host cells being by infection into prokaryotic host cells harbouring said second vectors, or said second vectors being packaged in infectious replicable genetic display packages

and their introduction into prokaryotic host cells being by infection into host cells harbouring said first vectors; and

(b) causing or allowing recombination between said first and second vectors within said prokaryotic host cells, the recombination being promoted by inclusion in said first and second vectors of sequences at which site-specific recombination occurs,

which sequences at which site-specific recombination occurs are derived from a loxP sequence, resulting in recombinant vectors each of which comprises nucleic acid encoding a said single chain specific binding pair member comprising a said first polypeptide chain component and a said second polypeptide chain component and an amino acid sequence encoded by a sequence provided by recombination between said sequences at which site-specific recombination occurs, and capable of being packaged into a replicable genetic display packages using said replicable genetic display package component;

(c) expressing said single chain specific binding pair members, producing replicable genetic display packages which display at their surface said single chain specific binding pair members and which each comprise nucleic acid encoding a said single chain specific binding pair member;

(d) selecting by binding with said complementary specific binding pair member of interest one or more single chain specific binding pair members specific for said complementary specific binding pair member of interest, each single chain specific binding pair member thus selected being associated in its respective replicable genetic display package with nucleic acid encoding that single chain specific binding pair member;

(e) obtaining nucleic acid encoding a single chain specific binding pair member from its replicable genetic display package displaying a specific binding pair member selected in step (d);

(f) producing, by expression of encoding nucleic acid in a recombinant host organism, a single chain specific binding pair member comprising a first polypeptide

chain component and a second polypeptide chain component and an amino acid sequence encoded by a sequence provided by recombination between said sequences at which site-specific recombination occurs and specific for said complementary specific binding pair member of interest, which single chain specific binding pair comprises a first polypeptide chain component which is as encoded by nucleic acid encoding a said first polypeptide chain component of a specific binding pair member selected in step (d) or is a derivative thereof by way of addition, deletion, substitution or insertion of one or more amino acids or by linkage of another molecule, and a second polypeptide chain component which is as encoded by nucleic acid encoding a said second polypeptide chain component of a specific binding pair member selected in step (d) or is a derivative thereof by way of addition, deletion, substitution or insertion of one or more amino acids or by linkage of another molecule.

2. A specific binding pair member according to claim 1 comprising an antibody antigen binding domain.

3. A specific binding pair member according to claim 2 which comprises a single chain Fv molecule.

4. A specific binding pair member according to claim 1 wherein said replicable genetic display packages are secreted bacteriophage.

5. A specific binding pair member according to claim 2 wherein said replicable genetic display packages are secreted bacteriophage.

6. A specific binding pair member according to claim 3 wherein said replicable genetic display packages are secreted bacteriophage.

7. A specific binding pair member according to claim 1 wherein the recombination takes place in a bacterial host which replicates phages or phagemids preferentially over plasmids.

8. A specific binding pair member according to claim 7 wherein said bacterial host is a PolA strain of *E. coli* or of another gram-negative bacterium.

9. A specific binding pair member according to claim 2 wherein the recombination takes place in a bacterial host which replicates phages or

phagemids preferentially over plasmids.

10. A specific binding pair member according to claim 9 wherein said bacterial host is a PolA strain of E. coli or of another gram-negative bacterium.

11. A specific binding pair member according to claim 3 wherein the recombination takes place in a bacterial host which replicates phages or phagemids preferentially over plasmids.

12. A specific binding pair member according to claim 11 wherein said bacterial host is a PolA strain of E. coli or of another gram-negative bacterium.

13. A specific binding pair member according to claim 4 wherein the recombination takes place in a bacterial host which replicates phages or phagemids preferentially over plasmids.

14. A specific binding pair member according to claim 13 wherein said bacterial host is a PolA strain of E. coli or of another gram-negative bacterium.

15. A specific binding pair member according to claim 5 wherein the recombination takes place in a bacterial host which replicates phages or phagemids preferentially over plasmids.

16. A specific binding pair member according to claim 15 wherein said bacterial host is a PolA strain of E. coli or of another gram-negative bacterium.

17. A specific binding pair member according to claim 6 wherein the recombination takes place in a bacterial host which replicates phages or phagemids preferentially over plasmids.

18. A specific binding pair member according to claim 17 wherein said bacterial host is a PolA strain of E. coli or of another gram-negative bacterium.

US-PAT-NO: 6017732

DOCUMENT-IDENTIFIER: US 6017732 A

TITLE: Bacteriophage library displaying immunoglobulin repertoires with a chemical moiety covalently bound within the binding site: production and selection thereof

DATE-ISSUED: January 25, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE
COUNTRY			
Jespers; Laurent	Tervuren	N/A	N/A
BEX			
Stephane Anne Therese	Cambridge	N/A	N/A
GBX			
Winter; Gregory Paul	Seattle	WA	N/A
N/A			
Bonnert; Timothy Peter	Bad	N/A	N/A
DEX			
Simon; Thomas Martin	Krozingen-Hausen		
US-CL-CURRENT: 435/69.6, 435/320.1, 435/472, 435/69.1, 435/69.7			
, 435/71.1, 530/350			
, 530/387.1, 530/387.3, 530/402			

CLAIMS:

We claim:

1. A diverse repertoire of first specific binding pair (sbp) members each having a binding site for second sbp member and each being fused to a surface component of a bacteriophage, wherein each first sbp member has a first polypeptide domain which comprises a binding region of immunoglobulin heavy chain variable domain (VH) and a second polypeptide domain which comprises a binding region of an immunoglobulin light chain variable domain (VL), the first and in that each binding site comprises a chemical moiety bound covalently at an amino acid residue within the binding site.
2. A method of providing a diverse repertoire of first specific binding pair (sbp) members each of which has a binding site and is fused to a surface component of a bacteriophage, each first sbp member having a first polypeptide domain which comprises a binding region of an immunoglobulin heavy chain variable domain (VH) and a second polypeptide domain which comprises a binding of an

immunoglobulin light chain variable domain (VL), the first and second polypeptide domains forming the binding site, the method being characterized by a step of chemical modification of first sbp members in the repertoire to introduce a chemical moiety bound covalently to an amino acid residue in the binding site of each first sbp member.

3. A method according to claim 2 wherein provision of the repertoire of first sbp members before the step of chemical modification comprises expression from a population of nucleic acid molecules collectively encoding the repertoire.

4. A method according to claim 3 wherein provision of the population of nucleic acid molecules comprises a step of mutation of nucleic acid encoding first sbp member, or a polypeptide component part thereof, to introduce a codon encoding the amino acid residue.

5. A method according to claim 2 wherein the amino acid residue is selectively modified in each first sbp member.

6. A method according to claim 2 wherein the population of nucleic acid molecules is provided by joining gene fragments.

7. A method according to claim 2 wherein the chemical modification is performed in vitro.

8. A method according to claim 2 comprising, following said chemical modification, a step of selection of a first sbp member with a binding site able to bind a second sbp member of interest.

9. A method according to claim 8 wherein the selection is by binding with second sbp member of interest.

10. A method according to claim 8 wherein binding of the selected first sbp member to the second sbp member of interest is enhanced compared with binding of that first sbp member without said chemical moiety.

11. A method according to claim 8 wherein binding of the selected first sbp member to the second sbp member of interest is dependent on the presence of the chemical moiety bound covalently at said amino acid.

12. A method according to claim 8 wherein the first sbp members are expressed fused

to a surface component of a bacteriophage so that each bacteriophage in a population thereof thereby displays a first sbp member at its surface, each bacteriophage in the population containing a nucleic acid molecule which encodes the first sbp member displayed at its surface.

13. A method according to claim 12 wherein selection of a first sbp member with a binding site able to bind a second sbp member of interest is followed by recovery of a sequence of nucleotides from the bacteriophage which displays the selected first sbp member on its surface.

14. A method according to claim 13 wherein the sequence of nucleotides is used in the production of a first sbp member with a binding site able to bind that second sbp member of interest.

15. A method of providing a genetically diverse repertoire of first specific binding pair (sbp) members each of which has a binding site for complementary second sbp member and is fused to a surface component of a bacteriophage, each first sbp member having a first polypeptide domain which comprises a binding region of an immunoglobulin heavy chain variable domain (VH) and a second polypeptide domain which comprises a binding region of an immunoglobulin light chain variable domain (VL) the first and second polypeptide domains forming the binding site, the method comprising:

provision of a population of nucleic acid molecules collectively encoding a genetically diverse repertoire of first sbp members, the binding site of the encoded first sbp members each having an amino acid residue which is selectively modifiable to introduce a covalently bound chemical moiety into the binding site; expression from the nucleic acid to provide a repertoire of first sbp members.

16. A method according to claim 15 wherein provision of the population of nucleic acid molecules comprises a step of mutation of nucleic acid encoding first sbp member, or a polypeptide component part thereof, to introduce a codon encoding the amino acid residue.

17. A method according to claim 15 wherein the population of nucleic acid molecules is provided by joining gene fragments.

18. A method according to claim 15 comprising chemical modification of first sbp members in the repertoire thereof at said amino acid residue to introduce a

covalently bound chemical moiety into the binding site.

19. A method according to claim 18 comprising, following said chemical modification, a step of selection of first sbp member with a binding site able to bind a second sbp member of interest.

20. A method according to claim 19 wherein the selection is by binding with second sbp member of interest.

21. A method according to claim 19 wherein binding of the selected first sbp member to the second sbp member of interest is enhanced compared with binding of that first

sbp member without said chemical moiety.

22. A method according to claim 19 wherein binding of the selected first sbp member to the second sbp member of interest is dependent on the presence of the chemical

moiety bound covalently at the amino acid.

23. A method according to claim 19 wherein the first sbp members are expressed fused to a surface component of a bacteriophage so that each bacteriophage in a population thereof thereby displays a first sbp member at its surface, each bacteriophage in the population containing a nucleic acid molecule which encodes the first sbp member displayed at its surface.

24. A method according to claim 23 wherein selection of a first sbp member with a binding site able to bind a second sbp member of interest is followed by recovery of a sequence of nucleotides from the bacteriophage which displays the selected first sbp member on its surface.

25. A method according to claim 24 wherein the sequence of nucleotides is used in the production of a first sbp member with a binding site able to bind that second sbp member of interest.